IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#13/a

In re Patent Application of:

BRAHMACHARI *et al.*

Application No.: 09/707,919

Filed: November 8, 2000

For: METHOD OF DETECTION OF ALLELIC VARIANTS OF SCA2 GENE

Attorney Docket No.: 39562-175772

Group Art Unit: 1645

Examiner: J.A. Goldberg

AMENDMENT

Customer No.

26694

PATENT TRADEMARK OFFICE

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action issued February 13, 2002 in the above-referenced application, please enter the following amendments and consider the following remarks. Please extend the time to respond by one month until June 13, 2002, for which purpose a check for the requisite fee is enclosed. Please charge any additional fee required or refund any overpayment to deposit account no., referencing 39562-175772.

IN THE SPECIFICATION:

Amend the specification as follows:

On pages 8-9, replace the paragraph beginning at the bottom of page 8 with the following:

a1

--Figure 1 is a schematic representation of the two novel single nucleotide polymorphisms in SCA2 gene. The top line depicts the position of the 25 exons of the SCA2 gene. The second line shows the relative locations of the two polymorphic sites

and the CAG repeat tract in exon 1 of SCA2 gene. Both the polymorphisms are also shown in sequence context below the gene. A depicts bases 10-19 of SEQ ID NO:10 and bases 10-19 of SEQ ID NO:9. B depicts bases 10-19 of SEQ ID NO:12 and bases 10-19 of SEQ ID NO:11.

On page 9, replace paragraphs 4-6 with the following three paragraphs:

--**Figure 4** shows the details of the SNP with reference ID 695871 submitted by the applicants in the SNP database.

Figure 5 shows the details of the SNP with reference ID 695872 submitted by the applicants in the SNP database.

Figure 6 shows the complete CDNA sequence of the human SCA2 MRNA submitted by pulst, S-M in the Genbank database.--

On page 10, replace the fourth paragraph with the following paragraph:

--(The applicants have already submitted these two SNPs in the SNP database on August 2, 2000. The first SNP at position 481 and having either a G or a C base have a reference SNP ID 695871. The reference SNP ID for the second SNP at position 552 and with T or a C base is 695872). --

On pages 10-11, replace the paragraph beginning at page 10, line 24 with the following:

--For example, the nucleotide sequence of the allelic variant of human SCA2 gene having polymorphic sites as listed in Table 1 may be-

5' C TCC GCC TCA GAC TGT TTT GGT AGC AAC GGC AAC GGC GGC GGC GCG TTT CGG CCC GGC TCC CGG CGG CTC CTT GGT CTC GGC GGG CCT CCC CGC CCC TTC GTC GTC CTC CTT CTC CCC CTC GCC AGC CCG GGC GCC CCT CCG GCC GCG CCA ACC CGC GCC TCC CCG CTC GGC GCC CGC GCG TCC CCG CCG CGT TCC GGC GTC TCC TTG GCG CGC CCG GCT CCC GGC TGT CCC CGC CCG GCG TGC GAG CCG GTG TAT GGG CCC CTC ACC ATG TCG CTG AAG CCC CAG CAG CAG CAG CAG CAG CAG CAG CAA CAG CAG

CAG CAG CAA CAG CAG CAG CAG CAG CAG CAG CAG CCG CCG CCC GCG GCT GCC AAT GTC CGC AAG CCC GGC GGC AGC GGC CTT CTA GCG TCG CCC GCC GCC GCG CCT TCG CCG TCC TCG TCC TCG GTC TCC TCG TCC TCG GCC AC 3' (SEQ ID NO:13)--

IN THE CLAIMS:

Cancel claims 1-9 without prejudice and enter the following claims:

--10. A method for predicting the susceptibility of an individual to human spinocerebellar ataxia 2 (SCA2 disease), said method comprising:

a) amplifying genomic DNA of SCA2 patients and normal control individuals using oligonucleotide primers for PCR amplification of CAG repeat-containing region of exon 1 of human SCA2 gene to obtain an amplified PCR product;

b) sequencing the amplified PCR product and identifying sequence variations computationally by comparing the product with known sequence of human SCA2 gene;

c) establishing the association of the CC and GT haplotype, as defined by the nucleotides present at positions 481 and 552, with SCA2 disease based on the haplotype frequency distribution in normal individuals and SCA2 patients;

d) repeating steps a) and b) on the genomic DNA of said individual; and

e) predicting the risk or susceptibility of said individual to SCA2 disease based on the haplotype present at the polymorphic sites in said individual, a GT haplotype being at low risk and a CC haplotype at high risk for the disease.

11. The method as claimed in claim 10 wherein the primers are selected from the group consisting of :

a) CTC CGC CTC AGA CTG TTT TGG TAG 3'(SEQ ID NO:1),

b) GTG GCC GAG GAC GAG GAG AC 3'(SEQ ID NO:2), and complements thereof.

12. A diagnostic kit for the detection of SNP haplotypes (CC/GT) comprising at least one primer and at least one probe selected from the group consisting of SEQ ID NO: 1 to 12.

13. An oligonucleotide primer consisting of a sequence selected from the group consisting of :

a) CTC CGC CTC AGA CTG TTT TGG TAG 3' (SEQ ID NO: 1); and

b) GTG GCC GAG GAC GAG GAG AC 3' (SEQ ID NO: 2) and complements thereof.

14. A method for predicting the susceptibility of an individual to human spinocerebellar ataxia 2 (SCA2) disease, said method comprising:

a) amplifying genomic DNA of said individual using oligonucleotide primers for PCR amplification of CAG repeat-containing region of exon 1 of human SCA2 gene to obtain an amplified PCR product;

b) sequencing the amplified PCR product and identifying sequence variations computationally by comparing the product with an established normal sequence for human SCA2 gene to determine whether said individual has a CC or GT haplotype; and

c) predicting the risk or susceptibility to SCA2 disease based on the haplotype present at polymorphic sites at nucleotide position 481 and 552 in the individual tested, a GT haplotype being at low risk and a CC haplotype at high risk for the disease.

15. The method of claim 14 comprising the additional steps of:

a) amplifying genomic DNA of SCA2 patients and normal control individuals using oligonucleotide primers for PCR amplification of CAG repeat-containing region of exon 1 of human SCA2 gene to obtain an amplified PCR product,

b) sequencing the amplified PCR product and identifying sequence variations computationally by comparing the product with an established normal sequence for human SCA2 gene to determine whether said individual has a CC or GT haplotype;

c) establishing the association of the CC and GT haplotype with SCA2 based on their frequency distributions in normal individuals and SCA2 patients;

d) statistically determining the risk of said individual for developing SCA2.

16. The method as claimed in claim 14 wherein the primers are selected from the group consisting of

a) CTC CGC CTC AGA CTG TTT TGG TAG 3'(SEQ ID NO:1);

b) GTG GCC GAG GAC GAG GAG AC 3'(SEQ ID NO:2); and complements thereof.

17. The method as claimed in claim 15 wherein the primers are selected from the group consisting of

a) CTC CGC CTC AGA CTG TTT TGG TAG 3'(SEQ ID NO:1);

b) GTG GCC GAG GAC GAG GAG AC 3'(SEQ ID NO:2); and complements thereof.--

REMARKS

With entry of this amendment, claims 10-16 are pending. Reconsideration is requested. The claims have been rewritten in accordance with the Examiner's helpful comments. Claims 10-16 are directed to the aspect of the invention of determining an individual's risk or susceptibility of developing SCA2 disease, oligonucleotide primers and kits. Support for the new claims can be found in the originally filed claims and throughout the specification. No new matter has been added.

The Examiner has objected to the disclosure because it contains hyperlinks on pages 9 and 10. The specification has been amended to delete these hyperlinks. The Examiner has also indicated that the SNPs indicated to be in bold at pages 10 and 11 are not visible. The bases in question have been underlined, in accordance with the Examiner's helpful suggestion. Withdrawal of the objection is respectfully requested.

The Examiner indicated that the sequence on page 10 and 11 is not included in the Sequence Listing. Paper and electronic copies of a new Sequence Listing are enclosed. The paper and electronic copies are identical and contain no new matter. Sequence

identifiers have been inserted at page 11 and on page 9 to indicate previously unidentified sequences.

Claims 2, 3, 4, 7, 8 and 9 were objected to for informalities. Claims 2, 3, 4, 7, 8 and 9 have been cancelled, thereby obviating the rejection. It is believed that the new claims are in acceptable form.

Claims 1-9 were rejected under 35 USC § 112, second paragraph, as being indefinite. Claims 1-5 were considered to be indefinite because they did not recite a positive process which clearly relates back to the preamble. It is believed that the newly entered claims are free of this portion of the rejection.

The Examiner considered the use of "polymorphic sites" and "variants" in the claims to be confusing. It is intended that these terms have the same meaning. The claims have been amended to recite "polymorphic sites" throughout. Withdrawal of this portion of the rejection is respectfully requested.

Claims 1, 2, 4, 7, 8 and 9 were considered indefinite because of improper Markush Groups. It is believed that the newly entered claims are free of this rejection.

Claim 3 was considered indefinite because the recitation "the allele specific primers" lacked antecedent basis. Claim 3 has been cancelled, thereby rendering this rejection moot.

Claim 5 was considered indefinite due to the range 5 to 100 recited for primers and probes. Claim 5 has been cancelled, thereby rendering the rejection moot.

Claim 6 was considered indefinite because it was unclear whether the kit comprises any one, or more than one primer or probe. Claim 6 has been rewritten as claim 16, which requires at least one primer and at least one probe. Withdrawal of this portion of the rejection is respectfully requested.

Claims 8-9 were rejected under 35 USC § 102(b) as being anticipated by Imbert et al., and under 35 USC § 102(a) as being anticipated by Muzney et al. and Pulst et al. Claims 8-9 have been cancelled, thereby rendering these rejections moot.

Claims 7 was rejected under 35 USC § 103 as being unpatentable over Pulst et al. To the extent to which this rejection may be considered applicable to claim 13, which replaces claim 7, it is traversed for the following reasons. The primers used by Pulst are immediately upstream and downstream from the CAG repeat region, whereas the primers

of the present invention have been selected from a different region. There is nothing in Pulst that teaches or suggests the specific primers claimed in claim 13, which are selected specifically to amplify the polymorphisms that are detected by the method of the present invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim 6 was rejected under 35 USC § 103 as being unpatentable over Pulst et al. and further in view of Ahern. To the extent to which this rejection may be considered applicable to claim 12, which replaces claim 6, it is traversed for the following reasons. For the reasons detailed above, Pulst does not teach or suggest the primers or probes (SEQ ID NOS 1-12) that are included in the diagnostic kit of claim 12. Ahern does not remedy the deficiency of Pulst to suggest these sequences. Accordingly, it is respectfully submitted that claim 12 is not obvious from the combination of Pulst and Ahern. The kit of claim 12 includes specific components (a probe and primer) to detect an SCA2 allelic variant that applicants have determined is prognostic for developing SCA2 disease. There is no teaching in either of the cited references, either alone, or together, that would suggest such a kit. Withdrawal of the rejection is respectfully requested.

All objections and rejections having been addressed, it is respectfully submitted that the application is in condition for allowance, and Notice to that effect is respectfully requested.

Respectfully submitted,

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Ann S. Hobbs
Registration No. 36,830
VENABLE
P.O. Box 34385
Washington, D.C. 20043-9998
Telephone: (202) 962-4800
Telefax: (202) 962-8300